

# ***Pharmaceuticals as Environmental Contaminants: an Overview of the Science***

**Christian G. Daughton, Ph.D.**

*Chief, Environmental Chemistry Branch*

Environmental Sciences Division

National Exposure Research Laboratory

Office of Research and Development

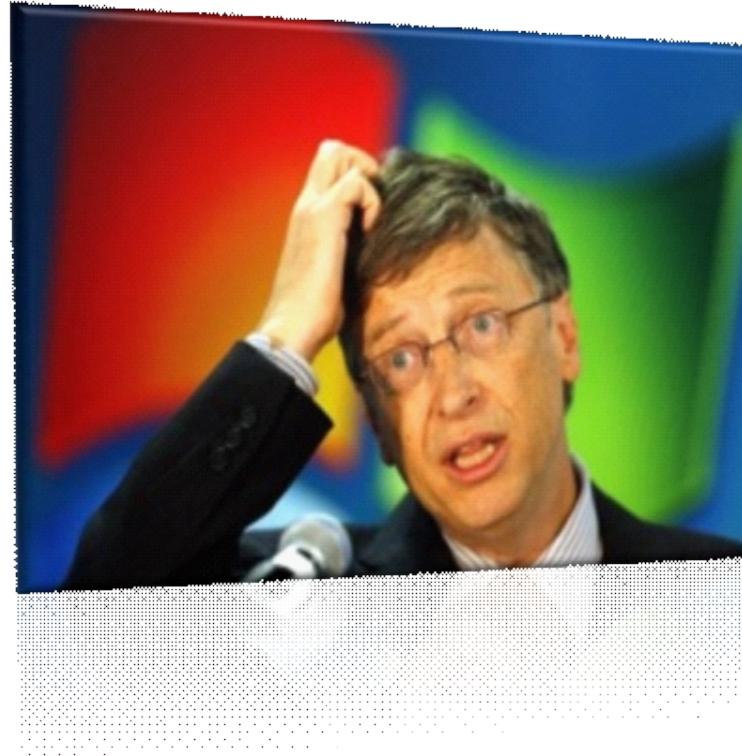
Environmental Protection Agency

Las Vegas, Nevada 89119

[daughton.christian@epa.gov](mailto:daughton.christian@epa.gov)



## *Why and how do drugs contaminate the environment?*



***What might it all mean?  
How do we prevent it?***

*This talk presents only a cursory overview of some of  
the many science issues surrounding the topic of  
pharmaceuticals as environmental contaminants*



## A Clarification

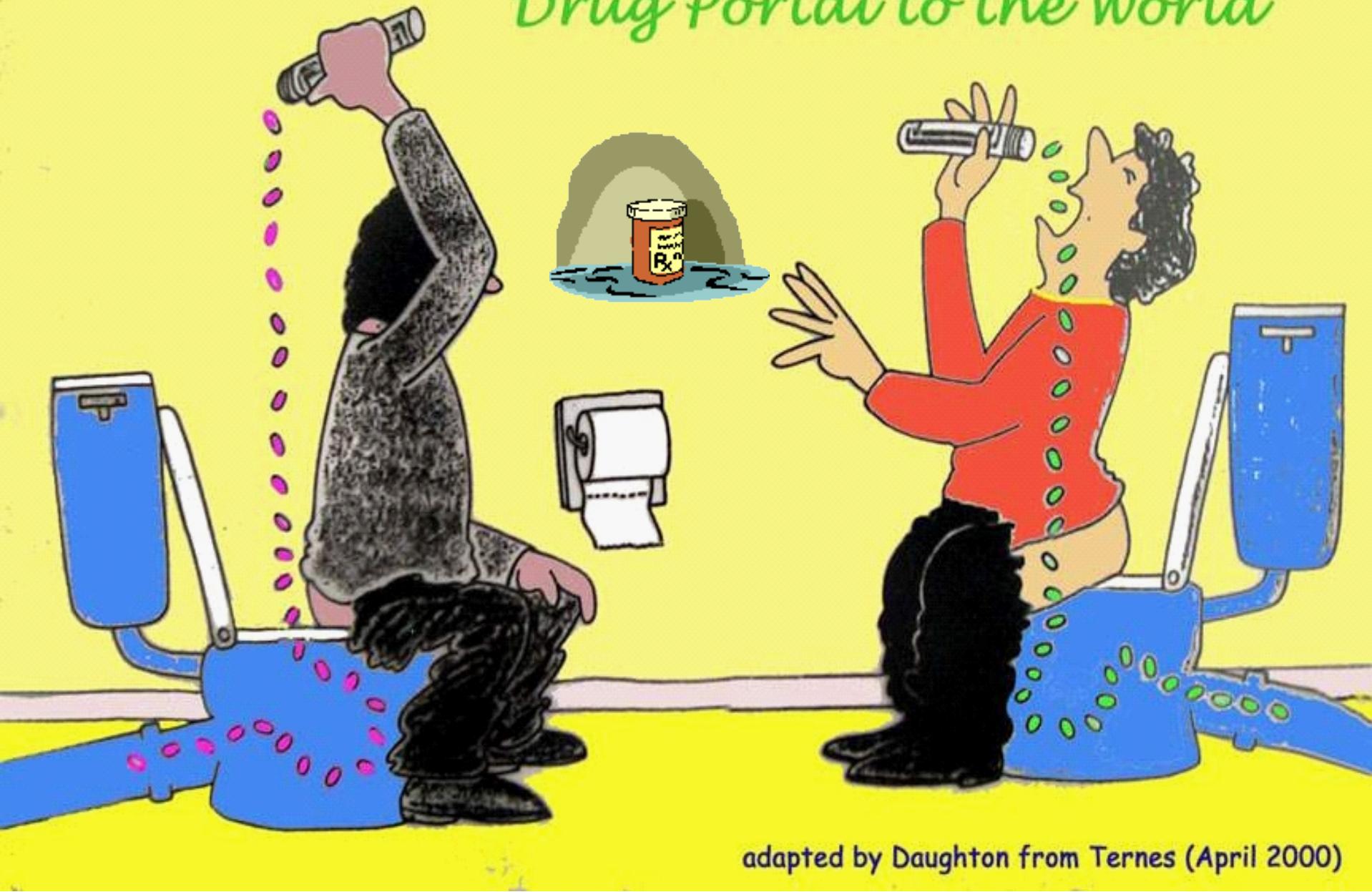
We sometimes loosely (but incorrectly) refer to **drugs, medicines, medications, or pharmaceuticals** as being the substances that contaminant the environment.



The actual environmental contaminants, however, are the *active pharmaceutical ingredients* – **APIs**.

*These terms are all often used interchangeably*

# *Drug Portal to the World*



adapted by Daughton from Ternes (April 2000)

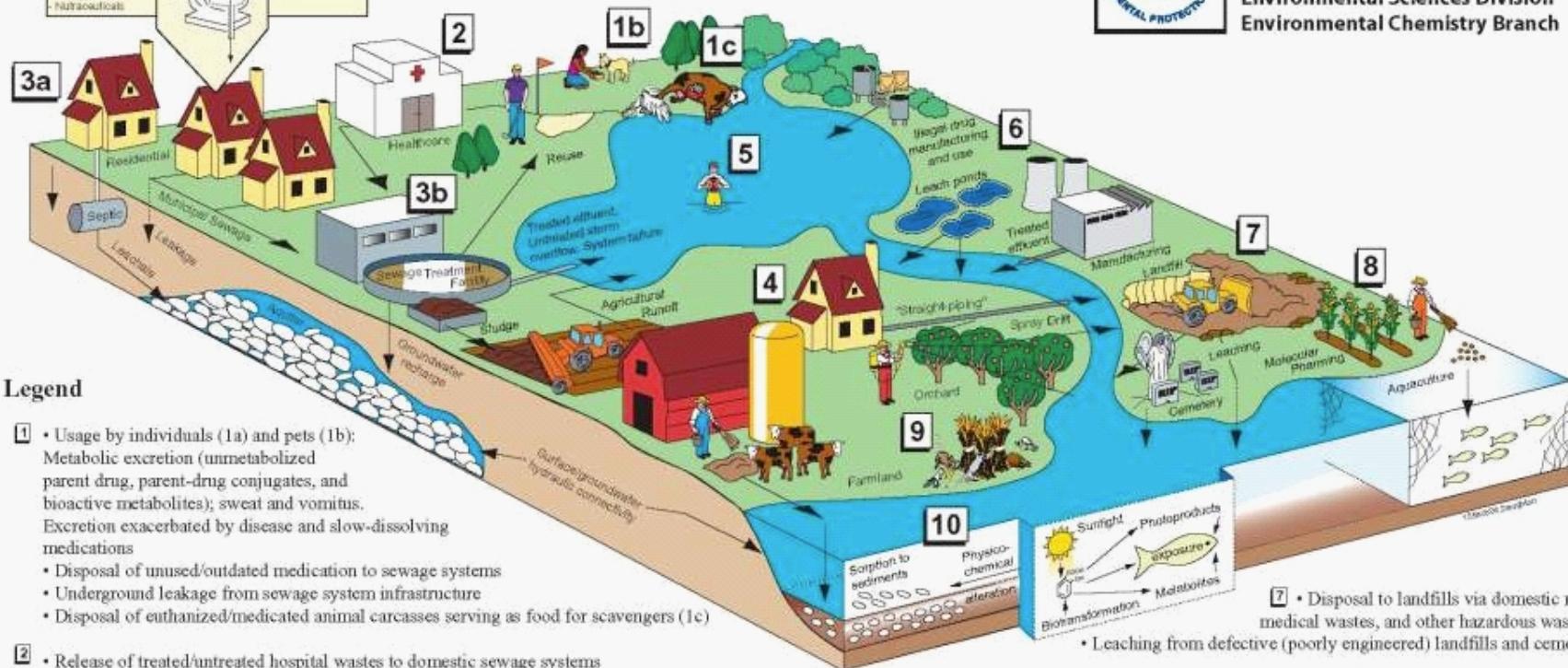


# Origins and Fate of PPCPs<sup>†</sup> in the Environment

'Pharmaceuticals and Personal Care Products



U.S. Environmental Protection Agency  
Office of Research and Development  
National Exposure Research Laboratory  
Environmental Sciences Division  
Environmental Chemistry Branch

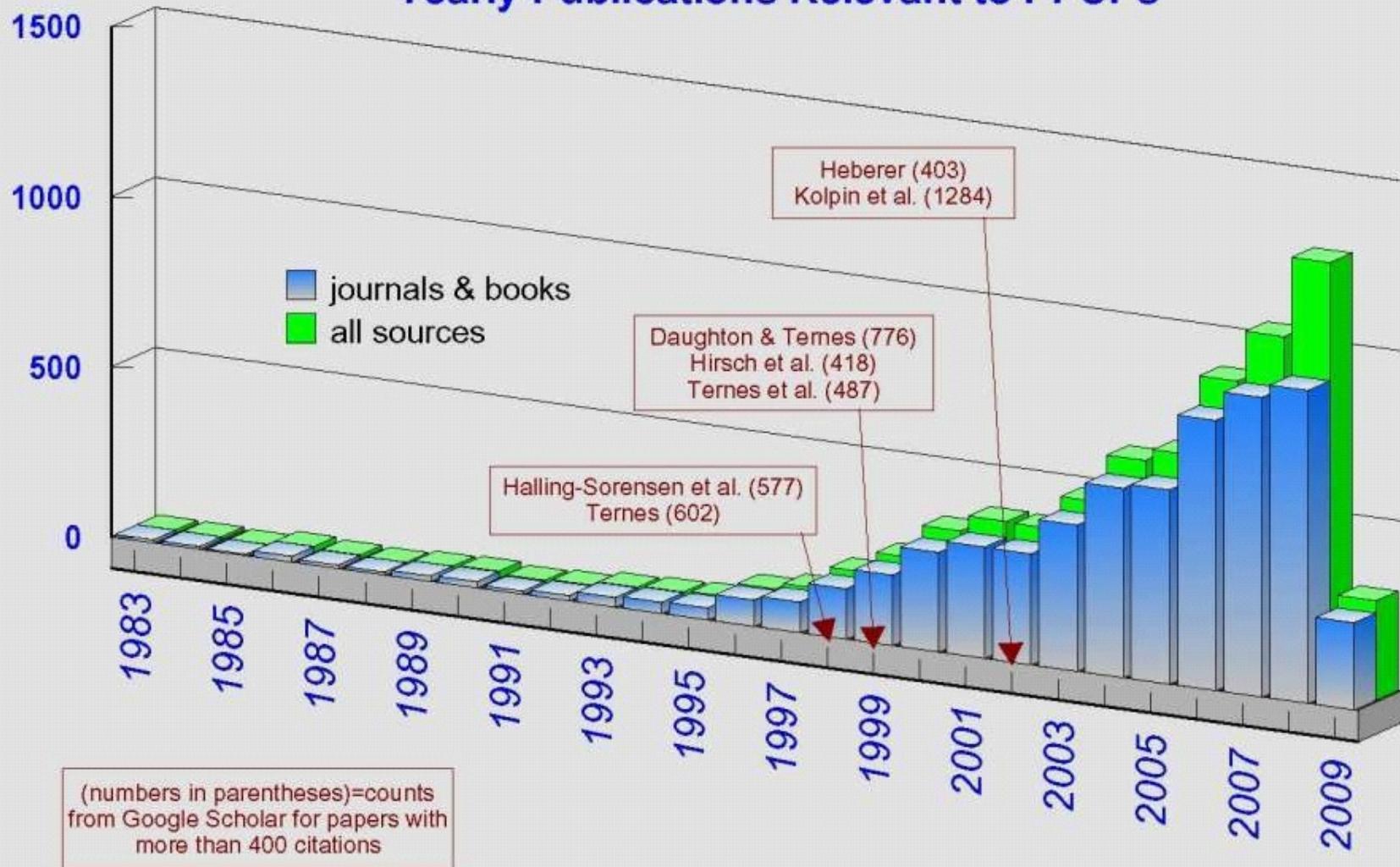


# Environmental Life-Cycle of Pharmaceuticals

created by CG Daughton  
US EPA, Las Vegas  
2 December 2006



## Yearly Publications Relevant to PPCPs



note: data for 2009 only through first 8 weeks

# The Chemical Universe

We live in a chemical sea of continually changing composition – comprising both anthropogenic and naturally occurring chemical stressors.

Unlike biota, chemical pollutants have no boundaries in their global distribution – “*everything is everywhere,*” only the concentrations vary.



# *The Chemical Universe*

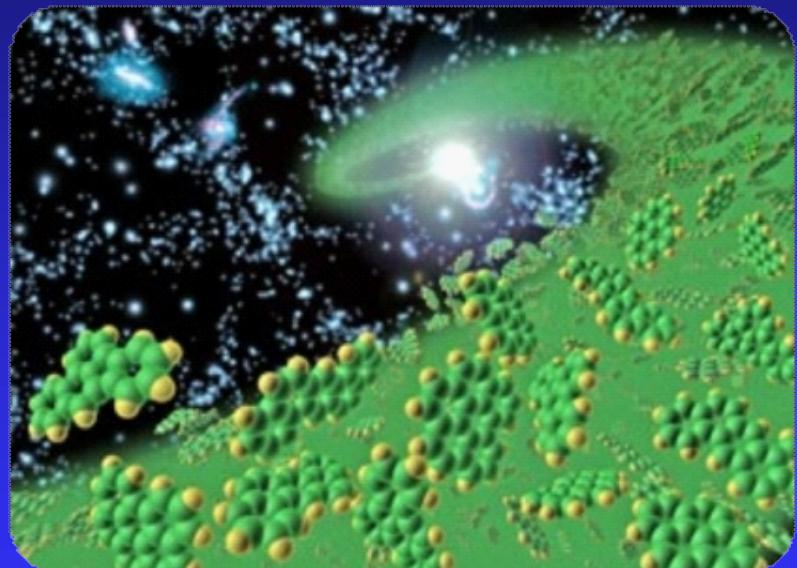
## **The *KNOWN* Universe**

As of September 2009, over 50 million organic and inorganic substances had been assigned CAS RNs.

(indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry; excluding bio-sequences such as proteins and nucleotides:

<http://www.cas.org/expertise/cascontent/registry/regsys.html>)

- Of these millions of known chemicals, nearly 35 million were commercially available.
- Of these, fewer than a quarter million (249,000) are inventoried or regulated by numerous government bodies worldwide -- representing about 0.7% of those that are commercially available or roughly 0.5% of the known universe of chemicals.
- Approximately 12,000 new substances are added each day.



# *The Chemical Universe*

The largest virtual chemical database yet reported comprises small drug-like molecules - - a total of over 977,000,000 structures (Blum and Reymond, 2009).

Restricted to organic molecules containing fewer than 14 atoms of C, N, O, and S (and limited types of Cl-substituted molecules). Excluded likely substituents such as F, Br, I, P, Si, metals, and most Cl.

Database represents the enormously large numbers of chemicals that could possibly be synthesized just from a very limited spectrum of types of elements and numbers of atoms.

Blum, L. C., and J.-L. Reymond. 2009. 970 Million Druglike Small Molecules for Virtual Screening in the Chemical Universe Database GDB-13. *J. Am. Chem. Soc.* 131 (25):8732-8733.

# *The Universe of Commercial APIs*

- Over 21,000 formulated drug products (ingredients, strengths, and form)
- **Over 1,460 FDA-approved small-molecule APIs** (molecularly distinct); oral >800, parenteral >420; topical >270
- Over 3,200 experimental drugs

Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. "DrugBank: a knowledgebase for drugs, drug actions and drug targets." *Nucl Acids Res* 2008, 36(suppl\_1):D901-906; doi:10.1093/nar/gkm958.

DrugBank PharmaBroswe web page:  
<http://www.drugbank.ca/pharmabrowse#mainB>.

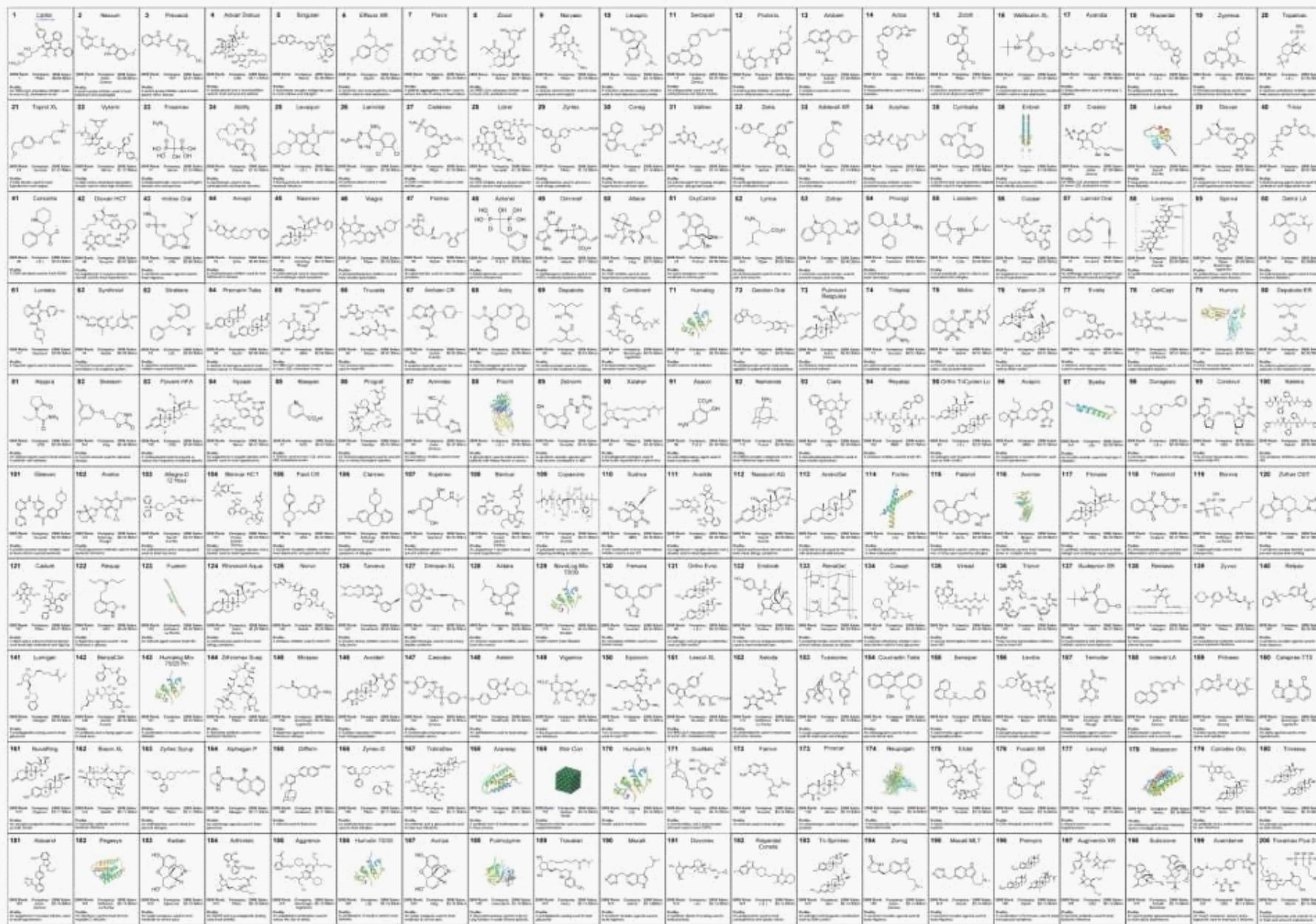


ALIMENTARY TRACT AND METABOLISM	Dolasetron	VITAMINS	Calcium Chloride	Amiloride	Felodipine	Flucytosine	Fluocinolone Acetonide	Tioconazole	Terazosin
METABOLIC PREPARATIONS	Granisetron	Paricalcitol	CARDIOVASCULAR	Cyclothiazide	Nitrendipine	Miconazole	Triamcinolone	Ketoconazole	Calcium Chloride
LAXATIVES	Ondansetron	Vitamin D4	SYSTEM CARDIAC	Furosemide	Perhexiline	Econazole	Flumethasone Pivalate	Miconazole	Finasteride
PREPARATIONS	Lactulose	(Dihydrotachysterol)	THERAPY	Eplerenone	Nifedipine	Sertaconazole	Hydrocortisone	Econazole	SYSTEMIC
Doxycycline	Magnesium Sulfate	MINERAL	Hydroflumethiazide	Bepридil	Ciclopirox	Mometasone	Hydrocortamate	Candidin	HORMONAL
Clotrimazole	Mannitol	SUPPLEMENTS	Phentermine	Indapamide	AGENTS ACTING ON	THE RENIN-ANGIOTENSIN SYSTEM	Clocortolone	Ciclopirox	PREPARATIONS, EXCL. SEX
Triamcinolone			Dofetilide	Chlorothiazide	PREPARATIONS FOR	TREATMENT OF WOUNDS AND ULCERS	Prednisolone	Clindamycin	HORMONES AND
Epinephrine	ANTIDIARRHEALS, INTESTINAL	Calcium Acetate	Midodrine	Bumetanide	OTHER	Methylprednisolone	OTHER	Carberoline	ASYLUS AND
Amphotericin B	Potassium Chloride	Magnesium Sulfate	Milrinone	Hydrochlorothiazide	VALSARTAN	Glycine	Cabergoline	Carboprost	HYPOTHALAMIC
Hydrocortisone	Calcium Chloride	Ranolazine	Trichlormethiazide	Ramipril	Isosorbide Dinitrate	Flucononide	Tromethamine	HORMONES AND	
Tetracycline		Disopyramide		Remikiren		Budesonide	Lisuride	Gonadorelin	ANALOGUES
Natamycin	AGENTS	Lidocaine	PERIPHERAL	Olmesartan Medoxomil	ANTIPURURITICS, INCL.	Dexamethasone	Naproxen	Nafarelin	
Chlorhexidine	Beclomethasone	Ibutilide Fumarate	VASODILATORS	Fosinopril	ANTI-HISTAMINES, ANESTHETICS, ETC.		Ritonavir	Carbetocin	
Metronidazole	Betamethasone	For systemic use	Mexiletine	Trandolapril					
Aspirin	Vancomycin	Oxandrolone	Phenylephrine	Benzacril					
Neomycin	Guamidine	Nandrolone	Digoxin	Tolazoline					
Minoxycline	Prednisone	Acetylglutoxitin	Acetyldiglotoxin	Enalapril					
Amlexanox	Nystatin	OTHER	Metaraminol	Lidocaine					
Miconazole	Amphotericin B	ALIMENTARY	Adenosine	Phentolamine					
Desamethasone	Hydrocortisone	TRACT AND METABOLISM	Epinephrine	Nicergoline					
DRUGS FOR ACID RELATED DISORDERS	Polymyxin B Sulfate	Nitisonone	Alprostadil	Tolazoline					
	Sulfasalazine	Miglustat	Fenoldopam	Isardipine					
	Natamycin	L-Carnitine	Dobutamine	Telmisartan					
	Pantoprazole	Loperamide	Cysteamine	Isosorbide Dinitrate					
	omeprazole			Sulfate					
	Prednisolone			Irbesartan					
	Sucralfate			Captopril					
	Neomycin	BLOOD AND BLOOD FORMING ORGANS	Levosimendan	ANTIPURURITICS					
	Lansoprazole	Balsalazide	Dopamine	Flumethasone Pivalate					
	Cimetidine	Diphenoxylate	Isosorbinide Mononitrate	Pentosan Polysulfate					
	Nizatidine	Streptomycin	Procainamide	LIPID MODIFYING AGENTS					
	Pirenzepine	Miconazole	Ticlopidine	Hydrocortisone	ANTI-HISTAMINES, ANESTHETICS, ETC.				
	Homatropine	Kanamycin	Ibuprofen	Perindopril					
	Methylbromide	Rifaximin	Argatroban	Desartarol					
	Esomeprazole	Budesonide	Treprostinal	Deslanoside					
	Ranitidine		Phenindione	Arbutamine					
	Famotidine		Fondaparinux sodium	Arimidarone					
	Misoprostol	ANTI-OBESITY PREPARATIONS, EXCL. DIET	Warfarin	Fluocinolone Acetonide					
	Rabeprazole	PRODUCTS	Clopidogrel	Flumethasone Pivalate					
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	Phentermine	Phenprocoumon	Propafenone	Pentosan Polysulfate					
	Fenfluramine	Dipyridamole	Tirofiban	LIPID MODIFYING AGENTS					
	Mazindol	Iloprost	Flecainide	AGENTS					
	Diethylpropion	Reserpine	Encainide	Procaine	ANTI-HISTAMINES, ANESTHETICS, ETC.				
	Oxyphenonium	Orlistat	Enoxaparin	Hydrocortisone					
	Oxyphenacylimine	Sibutramine	Bivalirudin	Perindopril					
	Hyoscymamine	Dexfenfluramine	Epoprostenol	Desartarol					
	Methylscopolamine			Desmopresside					
	Tridihexethyl			Minoxidil					
	Atropine			Timolol					
	Cisapride			Sotalol					
	Troglitazone			Carteolol					
	Diphemanil			Propranolol					
	Methylsulfate			Betalalol					
	Acarbose			Bisoprolol					
	Propantheline			Alprenolol					
	Methantheline			Pindolol					
	Alosetron			Carvedilol					
	Tegaserod			Acetubtol					
	Papaverine			Nadolol					
	Domperidone			Tolnaftate					
	Metoclopramide			Nystatin					
ANTIEMETICS AND ANTINAUSEANTS	Phenformin	BLOOD SUBSTITUTES AND PERfusion	Guanethidine	CALCIUM CHANNEL BLOCKERS	Naftifine	Fluconazole	Terconazole	Apomorphine	Terazosin
	Glipizide	Solutions	Rescinnamine	Isradipine	Halopropgin	Clotrimazole	Clotrimazole	Alprostadil	Sulfadiazine
	Nateglinide			Diltiazem	Natamycin	Chloramphenicol	Fluconazole	Tadalafil	Grepafloxacin
	Repaglinide			Amlodipine	Chlorphenene	Oxytetracycline	Furazolidone	Vardenafil	Ampicillin
				Nimodipine	Terbinafine	Quinonide	Butoconazole	Tolterodine	Penicillin V
				Nisoldipine	Ethanol	Sulfamethole	Beclomethasone	Oxybutynin	Cefpiramide
				Spironolactone	Tioconazole	Fluorometholone	Betamethasone	Dimethyl sulfoxide	Ceftazidime
				Lercanidipine	Ketoconazole	Butoconazole	Desoximetasone	Papaverine	Trimethoprim
				Neomycin	Verapamil	Fluticasone Propionate	Natamycin	Dutasteride	Chloramphenicol
				Metolazone	Butenafine			Flavoxate	Loracarbef



Azelastine	Olopatadine	Polymyxin B Sulfate	Aminohippurate	Pivalate	Lapatinib	Pivmecillinam
Promethazine	Polymyxin B Sulfate	Gentamicin	Aminophenazole	Dexmedetomidine	Lenalidomide	Podoflox
Mequitazine	Gentamicin	Prednisolone	Amobarbital	Dibucaine	Leucovorin	Posaconazole
Diphenhydramine	Tropicamide	Chlorhexidine	Amyl Nitrite	Dicumarol	Levallorphan	Practolol
Chlorpheniramine	Acetazolamide	Neomycin	Anisindione	Dicyclomine	Levomethadyl Acetate	Pranlukast
Diphenylpyraline	Natamycin	Oflloxacin	Anisotropine	Digitoxin	Levorphanol	Probucol
Cyclizine	Prednisolone	Dexamethasone	Methylbromide	Dimenhydrinate	Lincomycin	Procaterol
Bromodiphenhydramine	Dorzolamide		Ardeparin	Dimethylthiambutene	Lisdexamfetamine	Propercaine
Trimeprazine	Loteprednol Etabonate	VARIOUS ALL	Arformoterol	Diphenidol	Lopinavir	Quinacrine
	Chlorhexidine	OTHER	Azactidine	Divalproex sodium	Lubiprostone	Ramelteon
OTHER	Oxybuprocaine	THERAPEUTIC	Bacampicillin	Dromostanolone	Lumiracoxib	Rasagiline
RESPIRATORY	Rimexolone	PRODUCTS	Bambuterol	Drospirenone	Marimastat	Retapamulin
SYSTEM PRODUCTS	Bitamoprost	Hydroxocobalamin	Bentoquatum	Echothiopate Iodide	Mechlorethamine	Ridogrel
Nitric Oxide	Cocaine	Dexrazoxane	Benzphetamine	Edrophonium	Meclizine	Rifampin
Doxapram	Ketotifen Fumarate	Sevelamer	Benzquinamide	Enprofylline	Menthol	Rosoxacin
SENSORY ORGANS	Oxymetazoline	Pralidoxime	Benzthiazide	Ergonovine	Meperidine	Salbutamol
OPHTHALMOLOGIC	Demecarium bromide	Déferoxamine	Benzylpenicilloyl	Erythrityl Tetranitrate	Mephentermine	Salicylic acid
ALS	Netilmicin	Ethanol	Polylysine	Ethacrynic acid	Mesalazine	Salsalate
Vidarabine	Apraclonidine	Eddetic Acid	Bevantolol	Ethinamate	Metaxalone	Sitagliptin
Betaxolol	Azelastine	Phystostigmine	Befizafibrate	Ethiodized oil	Methacycline	Sodium lauryl sulfate
Erythromycin	Cyclopentolate	Amifostine	Bufenotene	Ethopropazine	Methimazole	Sorafenib
Alclometasone	Alclometasone	Naloxone	Butabarbital	Ethoxzolamide	Methotrimeprazine	Succinylcholine
Iodoxuridine	Nandrolone	Flumazenil	Butalbital	Ethyndiol Diacetate	Methylergonovine	Sulfametopyrazine
Medrysone	Neomycin	Fomepizole	Calcium Gluceptate	Fenoterol	Methylphenobarbital	Sulfisoxazole
Lidocaine	Ganciclovir		Candoxatril	Flouxuridine	Meticillin	Sulfoxone
Travoprost	Gatifloxacin	DIAGNOSTIC	Carbopoda	Flunirizepam	Metyrosine	Sunitinib
Morphine	Penicillin G	AGENTS	Carphenazine	Flupenthixol	Mifepristone	Telbivudine
Dapiprazole	Norfloxacin	Pentagastrin	Carprofen	Flurandrenolide	Mimosine	Temafloxacin
Fluorometholone	Streptomycin	Betazole	Cefalotin	Forasartan	Mitiglinide	Testolactone
Timolol	Emedastine	Ceruleotide	Cefazolin	Fosphenytoin	Molindone	Tetrahydrobiopterin
Phenylephrine	Pilocarpine	Bentiromide	Cefepime	Gamma Hydroxybutyric	Moricizine	Thiabendazole
Carbachol	Levocabastine	Inulin	Cefotetan	Mycophenolate mofetil	Thiamylal	
Ampicillin	Heparin	Gonadorelin	Cefpodoxime	Acid	Nafcillin	
Famiclovir	Levofloxacin	Magnesium Sulfate	Ceftibuten	Gentian Violet	Nelarabine	
Trifluridine	Dichlorphenamide	Histamine Phosphate	Cephaloglycin	Glibenclamide	Neostigmine	
Betamethasone	Ofloxacin	Metyrapone	Cephaloprin	Gliquidone	Nitazoxanide	
Chloramphenicol	Guanethidine	Tolbutamide	Cerulenin	Glutethimide	Nitrazepam	
Dipivefrin	Kanamycin		Cevimeline	Glycodiazine	Nitrofurazone	
Framycetin	Brinzolamide	CONTRAST MEDIA	Chloremerodrin	Glycopyrrolate	Norepinephrine	
Verteporfin	Levobunolol	Gadodiamide	Gadodiamide	Acid	Nafcillin	
Methylscopolamine	Metipranolol	Diatrizoate	Chloroxine	Guanabenz	Norethindrone	
Ketorolac	Dexamethasone	Gadoversetamide	Chlorthalidone	Guanadrel Sulfate	Novobiocin	
Amikacin		Gadoteridol	Halobetasol Propionate	Halobetasol Propionate	Olsalazine	
Brimonidine	OTOLOGICALS	Gadobenate	Cilastatin	Hesperetin	Omapatrilat	
Carteolol	Lidocaine	Cinalukast	Cilostazol	Hexafluorenium	Orciprenaline	
Ciprofloxacin	Betamethasone	Dimeglumine	Colchicine	Glycoprotein	Paliperidone	
Piroxicam	Chloramphenicol	dimeglumine	Colistimethate	Hydroxypropyl	Palonosetron	
Atropine	Hydrocortisone		Cinulakast	cellulose	Pamidronate	
Clomidine	Tetracycline	DIAGNOSTIC	Cinolazepam	Conivaptan	Paramethasone	
Sulfamethizole	Polymyxin B Sulfate	RADIOPHARMACEU	Clavulanate	Cromoglicate	Isethionate	
Diclofenac	Gentamicin	TICALS	Clenbuterol	Crotamiton	Hydroxyurea	
Oxytetracycline	Prednisolone	Succimer	Clidinium	Cryptenamine	Icodextrin	
Triamcinolone	Chlorhexidine		Cyclacillin	Cyclacillin	Emolast	
Sulfacetamide	Cocaine	UNCLASSIFIED	Cycloserine	Decamethonium	Imipenem	
Latanoprost	Neomycin	3-Methylthiofentanyl	Deferasirox	Indecainide	Perflutren	
Epinephrine	Miconazole	5-Methoxy-N,N-	Danazol	Indomethacin	Phenazopyridine	
Tobramycin	Dexamethasone	disopropyltryptamine	Darunavir	Iodoxanol	Phenindamine	
Fluorescein			Dasatinib	Iohexol	Pheniramine	
Methazolamide	OPHTHALMOLOGIC	Acpepromazine	Iophendylate	Iophendylate	Phenmetrazine	
Flurbiprofen	AL AND	Aciprometazine	Decamethonium	Iron Dextran	Penotolinium	
Nedocromil	OTOLOGICAL	Aciclovir	Decitabine	Isoetharine	Phenobarbital	
Procaine	PREPARATIONS	Afiskiren	Deferasirox	Isoflurophate	Phytomedicine	
Hydrocortisone	Betamethasone	Almitriptine	Delta-1-	Isoniazid	Picrotoxin	
Scopolamine	Chloramphenicol	Aleseroxyton	dihydrotestosterone	Isopropamide	Pipotiazine	
Epinastine	Ciprofloxacin	Alverine	Desonide	Isoproterenol	Pirbuterol	
Tetracycline	Tetracycline	Amdinocillin	Desoxycorticosterone	Josamycin	Pivampicillin	

# 200 Top-Selling Prescribed Drugs (2006)



## ***Routes of Entry to the Environment for APIs***

APIs are released to the environment by two primary routes:

### sewage:

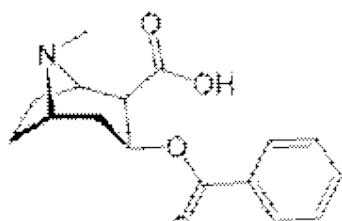
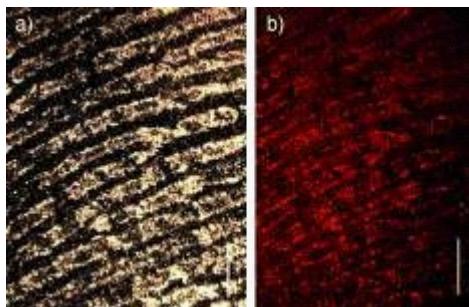
- excretion (as a function of pharmacokinetics)
- bathing (topically applied drugs and residues excreted via sweat)
- disposal to drains

### trash:

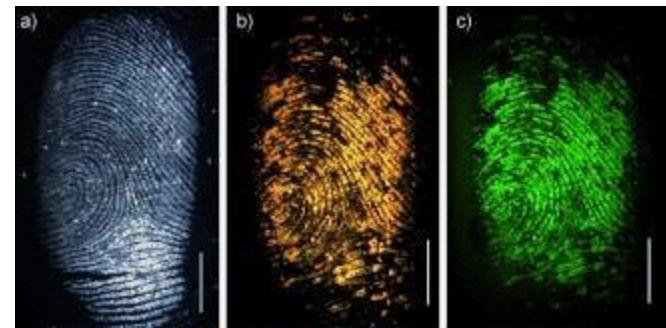
- discarding unwanted new medications
- as well as used delivery devices or containers with residuals



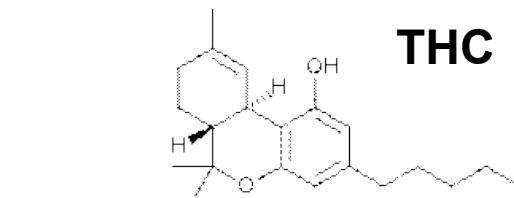
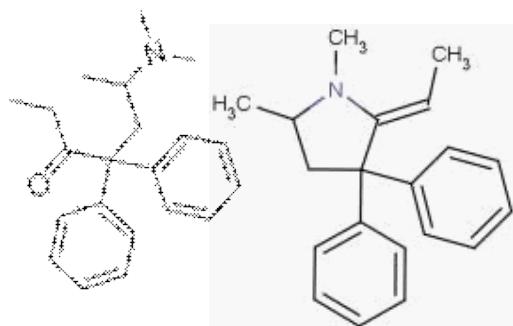
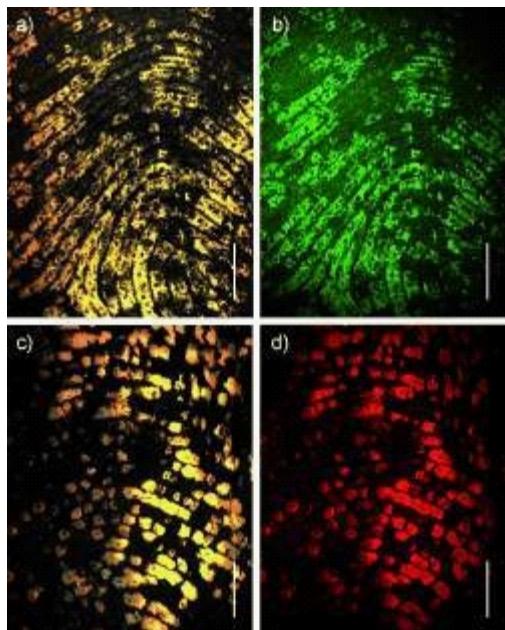
# Fingerprints as contributors of environmental contaminants



**benzoyllecgonine**



**methadone & EDDP**



*benzoyllecgonine* (major cocaine metabolite)

*EDDP*: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (major methadone metabolite)

*THC*: ? 9-tetrahydrocannabinol (main psychoactive of marijuana)

Hazarika P, Jickells SM, Wolff K, Russell DA (2008) Imaging of Latent Fingerprints through the Detection of Drugs and Metabolites. *Angew Chem Int Ed* 47:10167-10170.

# Sewage Treatment & Natural Attenuation

- Efficiency of API removal is highly variable – ranging from nearly complete to almost nil as a function of the API.
- Concentrations in treated sewage often range from 1-100 ng/L.
- “Removal” does not necessarily equate with “destruction” or with elimination of toxicity.
  - Parent (unchanged) APIs can partition to solid sludge.
  - Bioactive transformation products can be created.
  - API conjugates serve as hidden reservoirs of parent API.



# *Emerging Challenges Posed by Analytical Chemistry*

- Increasingly advanced methods of analysis allow peering into the shadows of chemical space with ever-greater magnification and clarity.
- In last 10 years, APIs in the environment can be detected below concentrations of 1 part-per-trillion (ng/L) - or the pM range.
- Ever-lower detection limits pose increasingly greater challenges for assessing, communicating, and ameliorating ever-diminishing risks.



# *Toxicity of Complex Environmental Mixtures: Poses Major Unanswered Questions*



Significance of long-term exposure to  
multiple APIs each present at levels  
below known effect levels

*While the focus of science has been on the potential for aquatic effects, the public and press primarily have been concerned with APIs in drinking water*



# *Effects on Aquatic Organisms: Cause for Concern*

- “Pseudo-persistence”
  - Continuous, multigenerational exposure
- Endocrine disruption (sub-ppb/ppt levels)
  - alterations to sexual differentiation
    - feminization; intersex
  - reproduction and growth impairments
    - Canadian lake study – EE2
    - subtle, behavioral effects - antidepressants
- More questions than answers



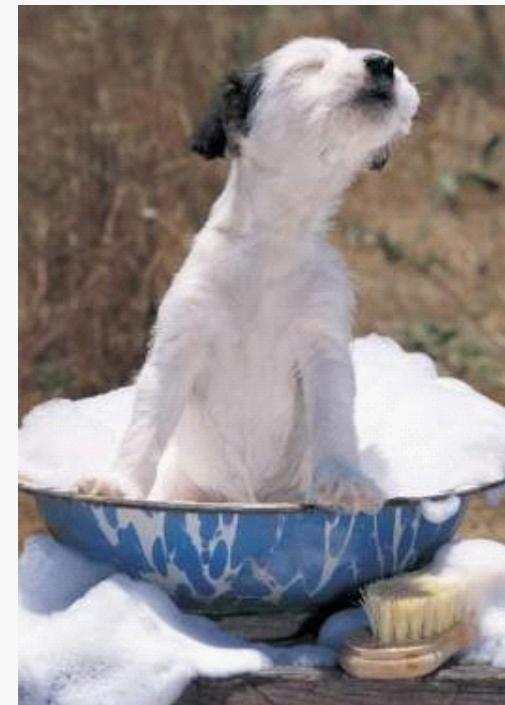
# The Potential for Human Health Effects

- Human exposure to APIs recycled from the environment via potable water is limited
- Extremely low concentrations (< 10 ng/L)
- Many APIs in source waters are removed by treatment
- Toxicological research restricted to *in vitro* studies and very limited epidemiological data.
- Concern focused primarily on vulnerable windows of exposure (e.g., fetal exposure) or to contraindicated APIs.
- Therapeutic levels are irrelevant (different mechanisms of action at ultra-low levels)



# *Significance of Disposal versus Excretion and Bathing*

- **Excretion:** continual low-level contributions of wide spectrum of APIs from multitudes of people
- **Bathing:** releases fewer types of APIs (medications applied directly to the skin and excreted via sweat) but at higher levels
- **Disposal:** acute but transient and episodic contributions from fewer people
  - Disposal is the only route that is most directly amenable to pollution prevention or source control measures
  - Proper disposal is greatly complicated by the conflict between the need to protect public safety and the need to minimize aquatic (and terrestrial) exposure



# **Major Unknown**

- **What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?**
  - No studies provided objective data from well-defined populations to support any type of conclusion
  - Data are needed on the types, quantities, and frequencies with which drugs accumulate and are disposed of as household waste



## Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-Month Period: Categorized by Therapeutic Class

<b>ATC Code</b>	<b>ATC Main Group</b>	<b>Quantity (mg) disposed</b>	<b>#of APIs</b>	<b>% of Total</b>
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Anti-infectives	5,608,735	45	10.4
M	Musculoskeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
<b>TOTAL</b>		<b>53,945,042</b>	<b>367</b>	

Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, 2008, 34(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available:  
<http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf>

# Drug Disposal: Major Unknowns

- Unknown: what types or quantities of APIs enter the environment via disposal.
- More importantly, it is not known what percentage of each API's environmental loading is contributed by disposal.
- Disposal could be significant for certain APIs and insignificant for others.
- This means that conscientious control of disposal may not lead to any detectable change in the environmental occurrence of many (or most) APIs.



# ***Drug Disposal: Major Unknowns***

- Significance of antibiotic residues in environment with respect to evolution of pathogen resistance
- Portion of human poisonings resulting from accidental ingestion and abuse of diverted drugs that are stored or disposed imprudently
- Prevention of diversion and human poisonings may be the more important driver for prudent disposal.



# Drug Disposal: Major Objectives

- An emphasis regarding disposal needs to be on protecting humans, pets, and wildlife from unintended acute exposures as a result of imprudent storage, stockpiling, or disposal of unwanted medications.
- Critical that guidance for disposal of drugs not jeopardize protection of human (or ecological) health.
- The ultimate objective, however, needs to be on reducing or eliminating the incidence of unwanted medications to begin with.



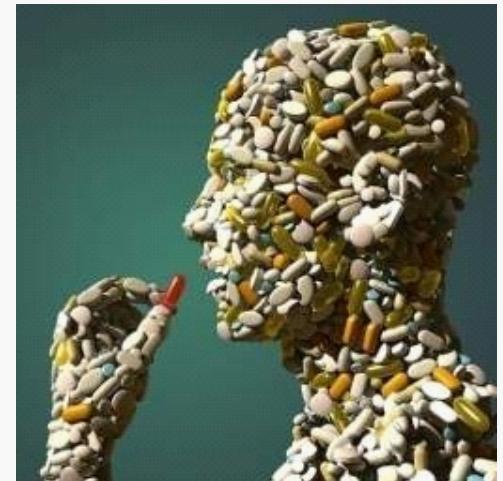
## Ultimate Objective: No Leftover Drugs

long-term focus should not be how to properly dispose of drugs, but rather *how to minimize, and ultimately eliminate the creation of drug waste*



# **Reducing Leftover Drugs**

- **Actions can be directed at improvements to any part of the life cycle of medications**, such as those spanning the vast, complex chain beginning with design/discovery, manufacturing, packaging, and advertising, and proceeding to prescribing (as also modified by practices of healthcare insurers) and dispensing, and ending with whether the medications are eventually consumed or used by the consumer.
- **Actions can be directed** not just at prudent alternatives for disposal, but **also (and more significantly) to reducing the contributions from excretion and bathing**.



## ***Actions to reduce APIs in the environment and protect human health & safety***

- Unit dosing
- Trial scripts
- Reduce polypharmacy
- Samples and donations
- Increased monitoring of patient
- Implement practice of concordance
- Personalized medicine (e.g., lower doses)
- Reduce incentives for excessive purchasing
- Low-quantity packaging of OTC medications
- Lower doses via non-racemic or deuterated APIs
- Prescribers to account for possible environmental impact
- Widespread implementation of sustainable take-back programs



# **Stewardship and Pollution Prevention**

## *Disposal control vs. Usage control:*

two basic approaches for reducing the entry of APIs to the environment

- **Disposal control:** prudent and environmentally sound engineered practices for disposal of unwanted medications.
- **Usage control:** prudent healthcare practices to minimize or optimize prescribing and dispensing of medications by eliminating unnecessary or imprudent customs.
- Significantly, **usage control perhaps has greater potential for reducing overall entry of APIs to the environment.** It can eliminate the need for disposal PLUS also minimize the residues that would otherwise be released by excretion and bathing.

## **Collateral Benefits to Pollution Prevention & Usage Control**

*In addition to reducing environmental contamination by APIs, prudent stewardship actions aimed at ensuring prudent, efficacious usage of medications might also:*

- **lessen healthcare costs** (via more effective treatment, reduced purchase costs, fewer prescribing/dispensing errors)
- **improve therapeutic endpoints and healthcare outcomes** (via better patient adherence/compliance)
- **reduce morbidity and mortality** caused by poisonings of infants, children, adults, pets, and sometimes wildlife by unused stored drugs or by drugs improperly disposed in trash.

# PharmEcovigilance

Conventional pharmacovigilance expanded beyond conventional focus on adverse drug reactions (ADRs) to encompass environmental concerns

Unify the parallel but interconnected needs for protecting both human and ecological health

# *Drug Disposal and Stewardship: Ramifications for the Environment and Human Health*



EPA publications on this topic:

<http://www.epa.gov/ppcp/projects/disposal.html>



# Questions

*feel free to contact:*

**Christian Daughton, Ph.D.**

Chief, Environmental Chemistry Branch

Environmental Sciences Division

National Exposure Research Laboratory

U.S. Environmental Protection Agency

Las Vegas, Nevada 89119

*daughton.christian@epa.gov*

702-798-2207

<http://www.epa.gov/nerlesd1/bios/daughton.htm>



# EPA Notice

*Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.*



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**Christian Daughton, Ph.D.**

Chief, Environmental Chemistry Branch  
Environmental Sciences Division  
National Exposure Research Laboratory  
U.S. Environmental Protection Agency

Las Vegas, NV 89119  
[daughton.christian@epa.gov](mailto:daughton.christian@epa.gov)  
702-798-2207

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